



Ference, B. A., Kastelein, J. J. P., Ray, K. K., Ginsberg, H. N., Chapman, M. J., Packard, C. J., Laufs, U., Oliver-Williams, C., Wood, A. M., Butterworth, A. S., Di Angelantonio, E., Danesh, J., Nicholls, S. J., Bhatt, D. L., Sabatine, M. S., & Catapano, A. L. (2019). Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants with Risk of Coronary Heart Disease. *JAMA - Journal of the American Medical Association*, 321(4), 364-373.
<https://doi.org/10.1001/jama.2018.20045>

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JAMA | Original Investigation

Association of Triglyceride-Lowering *LPL* Variants and LDL-C-Lowering *LDLR* Variants With Risk of Coronary Heart Disease

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IMPORTANCE Triglycerides and cholesterol are both carried in plasma by apolipoprotein B (ApoB)-containing lipoprotein particles. It is unknown whether lowering plasma triglyceride levels reduces the risk of cardiovascular events to the same extent as lowering low-density lipoprotein cholesterol (LDL-C) levels.

OBJECTIVE To compare the association of triglyceride-lowering variants in the lipoprotein lipase (*LPL*) gene and LDL-C-lowering variants in the LDL receptor gene (*LDLR*) with the risk of cardiovascular disease per unit change in ApoB.

DESIGN, SETTING, AND PARTICIPANTS Mendelian randomization analyses evaluating the associations of genetic scores composed of triglyceride-lowering variants in the *LPL* gene and LDL-C-lowering variants in the *LDLR* gene, respectively, with the risk of cardiovascular events among participants enrolled in 63 cohort or case-control studies conducted in North America or Europe between 1948 and 2017.

EXPOSURES Differences in plasma triglyceride, LDL-C, and ApoB levels associated with the *LPL* and *LDLR* genetic scores.

MAIN OUTCOMES AND MEASURES Odds ratio (OR) for coronary heart disease (CHD)—defined as coronary death, myocardial infarction, or coronary revascularization—per 10-mg/dL lower concentration of ApoB-containing lipoproteins.

RESULTS A total of 654 783 participants, including 91 129 cases of CHD, were included (mean age, 62.7 years; 51.4% women). For each 10-mg/dL lower level of ApoB-containing lipoproteins, the *LPL* score was associated with 69.9-mg/dL (95% CI, 68.1-71.6; $P = 7.1 \times 10^{-1363}$) lower triglyceride levels and 0.7-mg/dL (95% CI, 0.03-1.4; $P = .04$) higher LDL-C levels; while the *LDLR* score was associated with 14.2-mg/dL (95% CI, 13.6-14.8; $P = 1.4 \times 10^{-465}$) lower LDL-C and 1.9-mg/dL (95% CI, 0.1-3.9; $P = .04$) lower triglyceride levels. Despite these differences in associated lipid levels, the *LPL* and *LDLR* scores were associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (OR, 0.771 [95% CI, 0.741-0.802], $P = 3.9 \times 10^{-38}$ and OR, 0.773 [95% CI, 0.747-0.801], $P = 1.1 \times 10^{-46}$, respectively). In multivariable mendelian randomization analyses, the associations between triglyceride and LDL-C levels with the risk of CHD became null after adjusting for differences in ApoB (triglycerides: OR, 1.014 [95% CI, 0.965-1.065], $P = .19$; LDL-C: OR, 1.010 [95% CI, 0.967-1.055], $P = .19$; ApoB: OR, 0.761 [95% CI, 0.723-0.798], $P = 7.51 \times 10^{-20}$).

CONCLUSIONS AND RELEVANCE Triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

JAMA. 2019;321(4):364-373. doi:10.1001/jama.2018.20045

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All major clinical guidelines recommend treatment to lower plasma low-density lipoprotein cholesterol (LDL-C) because numerous randomized trials have demonstrated that therapies that lower LDL-C levels by reducing LDL particles through upregulation of the LDL receptor (*LDLR*) reduce the risk of cardiovascular events.¹⁻⁵ By contrast, the guidelines do not recommend treatment to lower plasma triglyceride levels because randomized trials have not provided consistent evidence that lowering plasma triglyceride levels reduces the risk of cardiovascular events.^{1,2}

Several novel therapies that potentially reduce triglyceride levels are currently in development.⁶⁻⁸ The development of these therapies has been motivated in part by the observation that rare loss-of-function mutations in the lipoprotein lipase (*LPL*) gene are associated with higher plasma triglyceride levels and a higher risk of cardiovascular disease; while rare, loss-of-function mutations in the *APOC3*, *ANGPTL3*, and *ANGPTL4* genes, which encode for natural inhibitors of *LPL*, are associated with lower triglyceride levels and a corresponding lower risk of cardiovascular disease.⁹⁻¹³ However, it is unknown whether lowering plasma triglyceride levels by targeting the *LPL* pathway will reduce the risk of cardiovascular events.

Both triglycerides and cholesterol are carried in plasma by apolipoprotein B (ApoB)-containing lipoprotein particles. Because all ApoB-containing lipoproteins, including triglyceride-rich lipoprotein particles and LDL particles, have a single ApoB molecule the clinical benefit of lowering triglyceride levels can be compared with the clinical benefit of lowering LDL-C levels by estimating their effects per unit change in ApoB. Therefore, the objective of this study was to use mendelian randomization to compare the association of triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants with the risk of cardiovascular disease per unit difference in ApoB to make inferences about the potential clinical benefit of lowering plasma triglyceride levels as compared with lowering LDL-C levels.

Methods

Study Population

The study included individual participant data from 367 641 participants enrolled in the UK Biobank study, individual participant data from 102 837 participants enrolled in 1 of 14 prospective cohort or case-control studies that reported data on cardiovascular outcomes in the US National Center for Biotechnology Information Database of Genotypes and Phenotypes program (dbGAP), and summary-level data from 184 305 participants enrolled in 1 of 48 prospective cohort, case-control, or cross-sectional studies included in the Coronary Artery Disease Genomewide Replication and Meta-Analysis plus the Coronary Artery Disease (CARDIoGRAMplusC4D) Consortium.¹⁴⁻¹⁶ Participants of European descent in the UK Biobank, and all racial/ethnic groups for which cardiovascular data were reported in the dbGAP and CARDIoGRAMplusC4D Consortium studies, were included in the analysis. In each included study, race/ethnicity was self-identified using a study-specific fixed-category questionnaire and was recorded to allow assessment of potential heterogeneity of effect estimates by ethnicity.

Key Points

Question What is the clinical benefit of lowering plasma triglyceride levels compared with lowering low-density lipoprotein cholesterol levels?

Findings In mendelian randomization analyses involving 654 783 participants, triglyceride-lowering variants in the lipoprotein lipase gene and low-density lipoprotein cholesterol (LDL-C)-lowering variants in the LDL receptor gene were associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of apolipoprotein B (ApoB)-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively).

Meaning The clinical benefit of lower triglyceride levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles.

Contributing studies received ethical approval from their respective institutional review boards, and written informed consent was obtained from all participants. A description of the included studies and the genotyping platforms used in each study is provided in eTable 1 in the Supplement.

Genetic Instruments

The *LPL* genetic score was constructed by combining all variants within 100kb on either side of the *LPL* gene that were associated with plasma triglyceride levels at genome-wide level of significance ($P < 5.0 \times 10^{-8}$) as reported by the Global Lipids Genetics Consortium and that were in low linkage disequilibrium ($r^2 < 0.3$) with all other variants included in the score.^{17,18} The *LDLR* genetic score was constructed similarly by combining all variants within 100kb on either side of the *LDLR* gene that were associated with plasma LDL-C levels at genome-wide level of significance and that were in low linkage disequilibrium ($r^2 < 0.3$) with all other variants included in the score. The exposure allele for each *LPL* variant was defined as the allele associated with lower plasma triglyceride levels, and the exposure allele for each *LDLR* variant was defined as the allele associated with lower LDL-C levels.^{17,18} For each participant, an *LPL* genetic score was calculated by summing the number of triglyceride-lowering alleles that participants inherited at each variant included in the *LPL* score and an *LDLR* score was calculated by summing the number of LDL-C-lowering alleles that participants inherited at each variant included in the *LDLR* score. Participants were excluded if they had missing data for 1 or more variants included in either genetic score.

Study Outcomes

The primary clinical outcome was coronary heart disease (CHD) defined as a composite of prevalent or the first incident occurrence of myocardial infarction (MI), coronary revascularization, or coronary death. For analyses involving individual participant data, the primary clinical outcome was harmonized across all included studies. For analyses involving summary-level data, the definition of CHD was defined by each study included in the CARDIoGRAMplusC4D consortium, which included CHD death, MI, and coronary revascularization but

in some studies also included chronic stable angina or more than 50% stenosis in a major epicardial coronary artery.¹⁶

Study Design and Statistical Analysis

A description of the study design, analyses performed, and data used for each analysis is provided in eFigures 1-3 in the [Supplement](#). The association of each genetic score with plasma triglycerides, LDL-C, and ApoB was evaluated using linear regression and with CHD risk using logistic regression. All regression analyses were performed separately in each of the included studies adjusting for age, sex, and the first 5 principal components of ancestry. To directly compare the clinical benefit of lower triglyceride levels due to the *LPL* score with lower LDL-C levels due to the *LDLR* genetic score, the associations of each score with risk of CHD was scaled for a common 10-mg/dL lower level of ApoB-containing lipoproteins. For individual participant data, the scaled point estimates were obtained by weighting each variant included in either genetic score by its associated change in ApoB. For summary-level data, the scaled associations were obtained by dividing the reported point estimate (and standard error) for an outcome by the reported point estimate for ApoB (measured in mg/dL). The scaled summary point estimates for all variants included in a score were then combined in a fixed-effect inverse variance-weighted meta-analysis to estimate the association between that genetic score generated using summary data and the outcome for a 10-mg/dL lower level of ApoB-containing lipoproteins.

The point estimates derived from the individual participant data and the summary data were then combined across studies in a fixed-effect inverse variance-weighted meta-analysis to produce an overall summary point estimate using a previously reported method that accounts for correlation between variants.¹⁹

Effect modification between lowering triglyceride levels through the *LPL* pathway and lower LDL-C levels through the LDL receptor pathway was assessed by comparing the associations of each genetic score with the risk of CHD stratified by the other genetic score. The association of combined exposure to triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants with the risk of CHD was evaluated in a 2 × 2 factorial mendelian randomization analysis.²⁰⁻²³ For both the stratified and factorial analyses, associations with the risk of CHD were necessarily restricted to participants with individual data and associations with changes in triglycerides, LDL-C, and ApoB were necessarily restricted to participants with individual data for whom 1 or more lipid measurements were available.

Sensitivity Analyses

To compare the potential clinical benefit of pharmacologically lowering triglyceride and LDL-C levels, the associations of the *LDLR* and *LPL* scores with the risk of CHD per unit difference in ApoB were compared with variants in the genes that encode the targets of current therapies that lower LDL-C through the LDL receptor pathway; variants in the genes that encode the targets of potential therapies that lower triglycerides through the *LPL* pathway; and variants in the *APOB* gene. To compare the association of triglyceride and LDL-C levels with the risk of CHD per unit difference in ApoB not related to

the *LPL* and *LDLR* genes, several additional genetic scores were constructed using up to 178 genetic variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium.^{17,18}

To further assess the independent associations of lower triglycerides, lower LDL-C, and lower ApoB on the risk of CHD, a multivariable mendelian randomization analysis was performed using these 178 genetic variants combined with the *LPL* and *LDLR* variants. This analysis was performed using meta-regression analyses in which the dependent variable was the associated log-odds for the risk of CHD, and the independent variables were the reported differences in plasma triglycerides, LDL-C, and ApoB for each variant included in the analysis, weighted by the inverse of the squared standard error for the association of each variant with CHD and forced to pass through the origin.

All analyses were performed using Stata (version 14.2; StataCorp), R (version 3.2.2; R Project for Statistical Computing), or Golden Helix SNP & Variation Suite software (version 8.1.4). A 2-tailed *P* value less than .05 was considered statistically significant. A detailed description is provided in eMethods in the [Supplement](#).

Results

Participant Characteristics

A total of 654 783 participants, including 91 129 cases of CHD, were included in the analysis (mean age, 62.7 years; 51.4% women). Individual participant data were available for 470 478 participants including 30 328 cases of CHD (Table 1). Summary-level data were available for a further 184 305 participants, including 60 801 cases of CHD.

LPL and *LDLR* Genetic Scores

A total of 5 independently inherited variants were included in the *LPL* score (eTables 2 and 3 in the [Supplement](#)) and 3 independently inherited variants were included in the *LDLR* score (eTables 4 and 5 in the [Supplement](#)). Each exposure allele in the *LPL* score was associated with an inverse variance-weighted mean of 11.64-mg/dL (95% CI, 10.38-10.90; $P = 8.3 \times 10^{-1365}$) lower plasma triglyceride level (to convert to mmol/L, multiply by 0.0113), 0.11-mg/dL (95% CI, 0.00-0.21; $P = .04$) higher plasma LDL-C level (to convert to mmol/L, multiply by 0.0259, and a 1.72-mg/dL (95% CI, 1.30-2.14; $P = 5.5 \times 10^{-16}$) lower level of ApoB-containing lipoproteins. By contrast, each exposure allele in the *LDLR* score was associated with an inverse variance-weighted mean of 3.42-mg/dL (95% CI, 3.27-3.57; $P = 2.3 \times 10^{-464}$) lower plasma LDL-C level, 0.48-mg/dL (95% CI, 0.03-0.93; $P = .04$) lower plasma triglyceride level, and a 2.40-mg/dL (95% CI, 2.02-2.79; $P = 3.9 \times 10^{-34}$) lower level of ApoB-containing lipoproteins.

Association of Genetic Scores With Lipids and CHD per Unit Change in ApoB

For each 10-mg/dL lower level of ApoB-containing lipoproteins, the *LPL* score was associated with 69.9-mg/dL (95% CI, 68.1-71.6; $P = 7.1 \times 10^{-1363}$) lower plasma triglyceride levels and

0.7-mg/dL (95% CI, 0.03-1.4; $P = .04$) higher plasma LDL-C level (Figure 1). By contrast, for the same 10-mg/dL lower level of ApoB-containing lipoproteins, the *LDLR* score was associated with 14.2-mg/dL (95% CI, 13.6-14.8; $P = 1.4 \times 10^{-465}$) lower plasma LDL-C level and 1.9-mg/dL (95% CI, 0.1-3.9; $P = .04$) lower plasma triglyceride level. Despite these differences in associated lipid levels, the *LPL* and *LDLR* scores were associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (odds ratio [OR], 0.771 [95% CI, 0.741-0.802], $P = 3.9 \times 10^{-38}$ for the *LPL* score and OR, 0.773 [95% CI, 0.747-0.801], $P = 1.1 \times 10^{-46}$ for the *LDLR* score). The associations of the *LPL* and *LDLR* scores with the risk of CHD per unit lower ApoB was consistent between studies that contributed individual participant data and studies that contributed summary data (eTable 6 in the Supplement).

In stratified analyses, the associations of the *LPL* and *LDLR* scores with plasma lipids, lipoproteins, and the risk of CHD appeared to be independent of each other (*LPL* score OR for CHD per 10-mg/dL lower ApoB, 0.771 [95% CI, 0.714-0.832] for participants with *LDLR* scores below the median and 0.769 [95% CI, 0.709-0.834] for participants with *LDLR* scores above the median) (eFigure 4 in the Supplement). In a 2×2 factorial mendelian randomization analysis, combined exposure to both the *LPL* and *LDLR* genetic scores was associated with linearly additive lower levels of triglyceride (*LPL* score alone: -20.1 mg/dL [95% CI, -28.8 to -13.3]; *LDLR* score alone: -3.8 mg/dL [95% CI, -15.1 to 7.3]; combined exposure to both scores: -24.3 mg/dL [95% CI, -32.4 to -16.2]), LDL-C levels (*LPL* score alone: -0.1 mg/dL [95% CI, -0.5 to 0.3]; *LDLR* score alone: -4.8 mg/dL [95% CI, -7.6 to -2.0]; combined exposure to both scores: -4.9 mg/dL [95% CI, -7.7 to -2.1]), and ApoB (*LPL* score alone: -3.0 mg/dL [95% CI, -4.9 to -1.2]; *LDLR* score alone: -3.4 mg/dL [95% CI, -5.2 to -1.5]; combined exposure to both scores: -6.4 mg/dL [95% CI, -8.5 to -4.4]), as well as a log-linearly additive decreases in the risk of CHD (*LPL* score alone: OR, 0.924 [95% CI, 0.889-0.960]; *LDLR* score alone: OR, 0.921 [95% CI, 0.885-0.958]; combined exposure to both scores: OR, 0.842 [95% CI, 0.811-0.874]) that was proportional to the absolute difference in ApoB but not to differences in either triglycerides or LDL-C (eFigure 5 in the Supplement).

Sensitivity Analyses

In additional analyses, variants in the genes that encode the targets for several potential therapies that lower triglycerides through the *LPL* pathway, and variants in the genes that encode the targets of several current therapies that lower LDL-C through the *LDLR* pathway, were also associated with similar lower risk of CHD per unit difference in ApoB as compared with the *LPL* and *LDLR* scores and as compared with an *APOB* score composed of 8 independently inherited variants in the *APOB* gene (Figure 2). Furthermore, the associated lower CHD risk for each of these variants and genetic scores was log-linearly proportional to their associated absolute lower level of ApoB-containing lipoproteins (Figure 3).

Several additional genetic scores consisting of other variants associated with triglycerides or LDL-C at genome-wide level of significance (excluding variants in the *LPL* and *LDLR* genes)—including scores consisting of variants associated with

Table 1. Baseline Characteristics of Study Participants^a

Characteristic	Participant Baseline Characteristics	No. of Participants With Available Data for Each Baseline Characteristic
Sample size, No.	654 783	654 783
CHD cases, No.	91 129	654 783
Age, mean (SD), y	62.7 (8.1)	654 783
Sex		
Women, No. (%)	336 462 (51.4)	654 783
Men, No. (%)	318 321 (48.6)	654 783
Blood pressure, mean (SD), mm Hg		
Systolic	132.1 (18.2)	470 478
Diastolic	80.9 (9.3)	470 478
Body mass index, mean (SD) ^b	27.5 (4.9)	470 478
Prevalent diabetes, No. (%)	21 642 (4.6)	470 478
Current smoker, No. (%)	43 284 (9.2)	470 478
Cholesterol, mean (SD), mg/dL		
Total	206.6 (39.4)	31 221
Low-density lipoprotein	129.7 (32.1)	31 221
High-density lipoprotein	52.0 (15.4)	31 221
Triglycerides, median (IQR), mg/dL	117.6 (84.1-163.3)	31 221
Apolipoprotein B, mean (SD), mg/dL	101.4 (27.3)	31 221
Non-high-density lipoprotein cholesterol (total cholesterol-HDL-C), mean (SD), mg/dL	154.9 (38.3)	31 221
Remnant cholesterol (total cholesterol-HDL-C-LDL-C), median (IQR), mg/dL	23.9 (15.9-32.8)	31 221

Abbreviations: CHD, coronary heart disease; IQR, interquartile range.

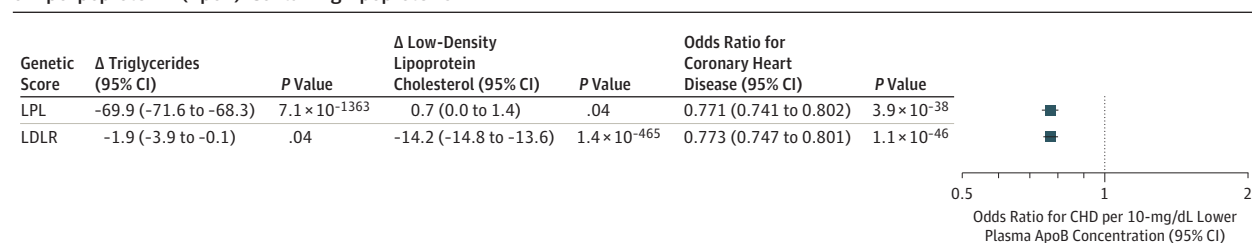
SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

^a Data for age and sex were available for all 654 783 participants included in the primary analysis. Data for other nonlipid baseline characteristics were available for 470 478 participants with individual-level data enrolled in the UK Biobank or 1 of the 14 case-control or cohort studies that reported cardiovascular outcomes in the database of genotypes and phenotypes program (dbGAP). Data for baseline lipid measurements were available for 31 221 participants with individual data enrolled in 1 of the dbGAP studies and for whom lipid measurements were available (the UK Biobank has not yet released lipid measurements of enrolled participants). Non-high-density lipoprotein cholesterol and remnant cholesterol levels are calculated values.

^b Calculated as weight in kilograms divided by height in meters squared.

either triglycerides or LDL-C; triglycerides but not LDL-C; LDL-C but not triglycerides; both triglycerides and LDL-C with the same direction of effect; and both triglycerides and LDL-C with opposite directions of effect—were also associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (Table 2). In multivariable mendelian randomization analyses that included both triglycerides and LDL-C in the same model, the associations between plasma triglycerides and LDL-C with the risk of CHD were independent and genome-wide significant. However, when changes in ApoB were included in these analyses, the associations between both plasma triglycerides and LDL-C with the risk of CHD became null (triglycerides: OR, 1.014 [95% CI, 0.965-1.065], $P = .19$;

Figure 1. Associations Between the Lipoprotein Lipase (*LPL*) and LDL Receptor Gene (*LDLR*) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins



Triglycerides are carried in plasma by ApoB-containing triglyceride-rich lipoproteins while cholesterol is carried predominantly by ApoB-containing low-density lipoproteins. Changes in plasma triglycerides and LDL-C concentration are thus markers of the corresponding changes in the concentration of the ApoB-containing lipoproteins that transport these lipids. Variants in the *LPL* gene that increase LPL activity are associated with lower triglycerides and a corresponding lower ApoB concentration, while variants in the *LDLR* gene that increase activity of the LDL receptor are associated with lower LDL-C and a corresponding lower ApoB. The figure shows that for each 10-mg/dL lower plasma ApoB concentration associated with variants in the *LPL* score, there is a corresponding 69.9-mg/dL lower triglyceride level, no change in LDL-C, and a lower risk of CHD (odds ratio, 0.771 [95% CI, 0.741-0.802]). By contrast,

for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the *LDLR* score, there is a corresponding 14.1-mg/dL lower LDL-C level, no change in triglycerides, and a similar lower risk of CHD (odds ratio, 0.773 [95% CI, 0.747-0.801]). Therefore, despite being associated with changes in different lipids, the *LPL* and *LDLR* scores were associated with similar lower risk of CHD for the same lower plasma ApoB concentration. The data presented are for the associations of the *LPL* and *LDLR* genetic scores with risk of CHD per 10-mg/dL decrease in ApoB-containing lipoproteins in all 654 783 participants included in the study. The associations of either score with changes in triglycerides and LDL-C per 10-mg/dL lower level of ApoB-containing lipoproteins are from up to 305 699 participants enrolled in the Global Lipid Genetics Consortium. Boxes represent effect size estimates and lines represent 95% CIs.

LDL-C: OR, 1.010 [95% CI, 0.967-1.055], $P = .19$; and ApoB: OR, 0.761 [95% CI, 0.723-0.798], $P = 7.51 \times 10^{-20}$ (Table 3; eTable 8 in the Supplement).

Discussion

In this study, triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants were associated with similar lower CHD risk per unit lower level of ApoB-containing lipoproteins. The associations between lower triglyceride level and lower LDL-C level with risk of CHD due to these variants appeared to be independent, additive, and proportional to the absolute change in ApoB. In addition, numerous variants in the genes that encode the targets of potential therapies that lower triglyceride levels through the *LPL* pathway and current therapies that lower LDL-C levels through the *LDLR* pathway were also associated with similar lower CHD risk per unit lower plasma ApoB levels. Furthermore, multiple genetic scores composed of other variants associated with either triglycerides, LDL-C, or both were also associated with similar lower risk of CHD per unit lower level of ApoB-containing particles, even when the associated changes in triglyceride and LDL-C levels were in opposite directions. In multivariable mendelian randomization analyses, the independent and genome-wide significant associations between triglycerides and LDL-C with the risk of CHD became null after adjusting for changes in ApoB.

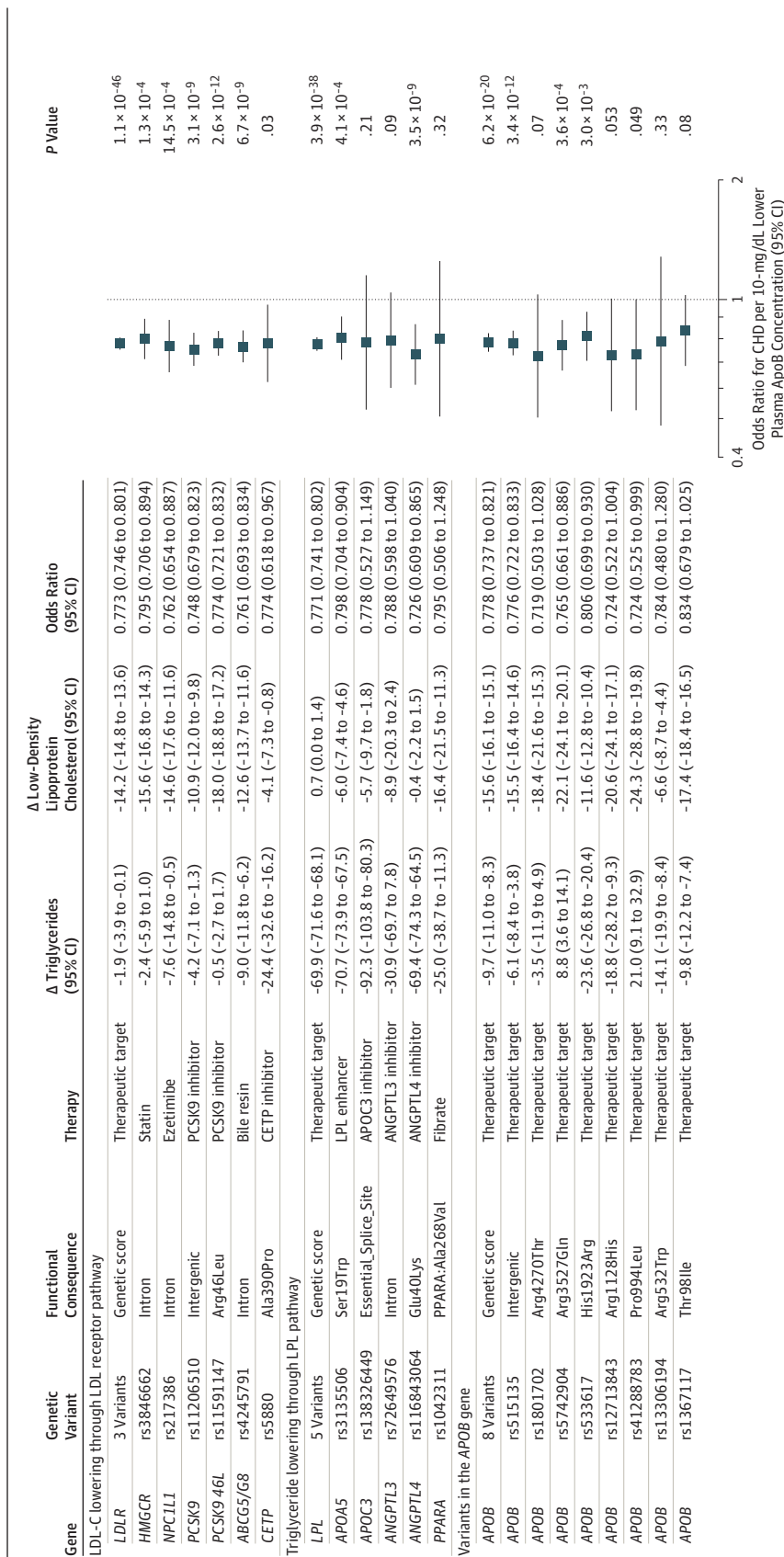
The results of this study suggest that the clinical benefit of lowering triglyceride levels is similar to the clinical benefit of lowering LDL-C levels per unit change in ApoB and is proportional to the net absolute reduction in ApoB-containing lipoproteins. The results of this study therefore suggest that all ApoB-containing lipoprotein particles, including triglyceride-rich very-low-density lipoprotein (VLDL) particles and their metabolic remnants as well as LDL particles, have approximately the

same effect on the risk of cardiovascular disease per particle. As a result, the clinical benefit of lowering triglyceride levels, lowering LDL-C levels, or lowering both may be proportional to the absolute change in ApoB-containing lipoproteins, regardless of the observed changes in plasma triglycerides or LDL-C.

The results of this study are consistent with the current understanding of the biology of lipids and atherosclerosis. Both triglycerides and cholesterol are carried in plasma by ApoB-containing lipoprotein particles. These particles are secreted by the liver as VLDL particles, which principally contain triglycerides, some cholesterol, and 1 molecule of ApoB. Lipoprotein lipase removes most of the triglycerides from these particles to convert the triglyceride-rich VLDL particles into triglyceride-depleted cholesterol-carrying LDL particles, which are then removed from plasma by hepatic LDL receptors. All ApoB-containing lipoproteins less than 70 nm in diameter, including triglyceride-rich VLDL remnants and LDL particles, freely flux across the endothelial barrier where they can become retained in the artery wall.²⁴ The cholesterol, and perhaps triglyceride, content of the ApoB particles retained in the artery wall provokes an inflammatory response that leads to the initiation and progression of atherosclerotic plaque.²⁵ The results of this study suggest that the effect of ApoB-containing particles on the risk of atherosclerotic cardiovascular disease appears to be determined largely by the concentration of circulating ApoB particles, which in turn determines the number of particles that become retained in the artery wall, regardless of whether those particles principally contain cholesterol or triglycerides. The present findings and interpretations based on mendelian randomization confirm and extend the initial findings and interpretations in 1980 of Sniderman and colleagues,²⁶ which were based on cross-sectional coronary angiographic studies.

The results of this study are also consistent with prior mendelian randomization studies demonstrating that triglyceride-rich ApoB-containing remnant particles appear to be causally

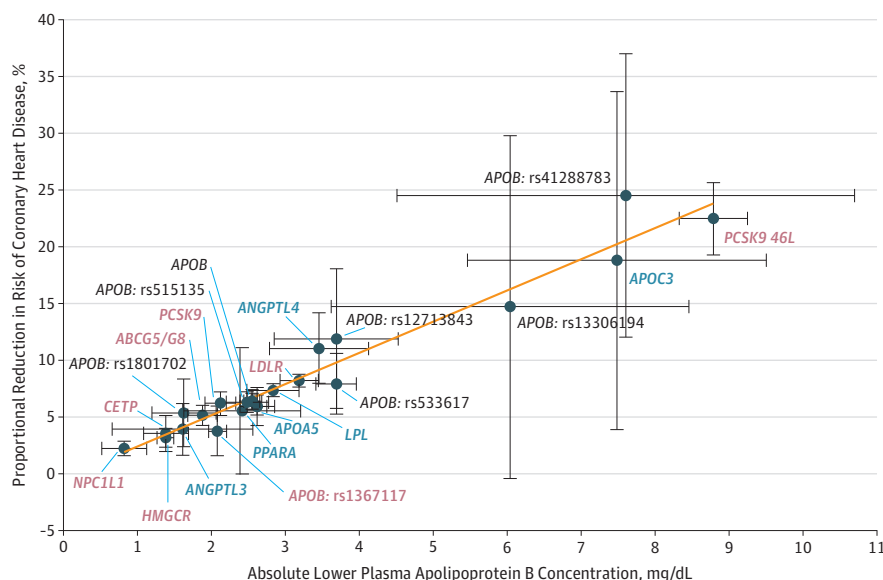
Figure 2. Association of Genetic Variants and Genetics Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins



Furthermore, for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the APOB gene score, there was a corresponding 9.7-mg/dL lower triglyceride level, 15.6-mg/dL lower LDL-C level, and a similar lower risk of CHD (odds ratio, 0.778 [95% CI, 0.737-0.821]). Despite a range of associated changes in triglycerides, LDL-C, or both, all genetic variants and genetic scores were associated with similar lower risk of CHD for the same 10-mg/dL lower plasma ApoB concentration. The APOB score is composed of the 8 independently inherited variants in the APOB gene listed in the figure. Boxes represent effect size estimates and lines represent 95% CIs. Associations with CHD per 10-mg/dL lower ApoB were measured in all 654 783 participants included in the study; associations with changes in triglycerides and LDL-C per 10-mg/dL lower ApoB were measured in up to 305 699 participants from the Global Lipid Genetics Consortium.

The figure shows the associations with triglycerides, LDL-C, and risk of CHD for the same 10-mg/dL lower ApoB-containing lipoprotein concentration for variants in the LPL and LDLR scores as compared with variants in the genes that encode the targets of current therapies that lower LDL-C through the LDL receptor pathway; variants in the genes that encode the targets of potential therapies that lower triglycerides through the LPL pathway; and variants in the APOB gene. For example, each 10-mg/dL lower plasma ApoB concentration associated with the partial loss-of-function rs1519147 variant in the PCSK9 gene was associated with a corresponding 18.0-mg/dL lower LDL-C level, no change in triglycerides, and a lower risk of CHD (odds ratio, 0.774 [95% CI, 0.721-0.832]). By contrast, for the same 10-mg/dL lower plasma ApoB concentration associated with the functional rs116843064 variant in the ANGPTL4 gene, there was a corresponding 69.4-mg/dL lower triglyceride level, no change in LDL-C, and a similar lower risk of CHD (odds ratio, 0.726 [95% CI, 0.609-0.865]).

Figure 3. Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease (CHD)



The associations of each genetic variant with ApoB concentration is plotted against its unadjusted association with CHD, expressed as a proportional lower risk (calculated as $[1 - OR_{CHD}] \times 100$). Variants in the genes that encode the targets of therapies that lower triglycerides through the LPL pathway are marked with blue labels, and variants in the genes that encode the targets of therapies that lower LDL-C through upregulation of the LDL receptor are marked with red labels. Circles represent the associated absolute change in ApoB

and corresponding proportional lower risk of CHD for each variant. The horizontal lines through each circle represent ± 1 standard errors for the associated absolute change in ApoB for each variant; and the vertical line through each circle represents ± 1 standard errors for the associated proportional lower risk of CHD. Associations with CHD were measured in all 654 783 participants included in the study; associations with ApoB were measured in a meta-analysis of 14 studies including up to 84 324 participants.

associated with the risk of cardiovascular disease.^{27,28} The results of the current study extend those findings by suggesting that triglyceride-rich remnant particles have approximately the same effect on the risk of cardiovascular disease as LDL particles. Furthermore, the results of this study are consistent with a recent mendelian randomization study that demonstrated that the causal effect of LDL particles on the risk of cardiovascular disease appears to be determined by the concentration of circulating LDL particles as measured by ApoB rather than by the mass of cholesterol carried by those particles as measured by LDL-C.²³ The results of the current study confirm and extend those findings by suggesting that the causal effect of all ApoB-containing lipoprotein particles on the risk of cardiovascular disease appears to be determined by the circulating concentration of those particles rather than by the mass of cholesterol or triglyceride that they carry.

The results of this study may also help to explain why prior randomized trials evaluating fibrates, which lower plasma triglyceride levels at least partially through the LPL pathway, have failed to consistently demonstrate that lowering triglyceride levels reduces the risk of cardiovascular events.²⁹⁻³³ The concentration of triglyceride-rich lipoproteins can be estimated by dividing plasma triglyceride concentration by 5 (on the mg/dL scale). Therefore, if all ApoB-containing particles have approximately the same atherogenic effect as suggested by this study, then to reduce the risk of cardiovascular events by 20% as can be achieved by lowering LDL-C levels by 40 mg/dL,^{3,4} triglyceride levels must be reduced by 5-fold this quantity, or approximately 200 mg/dL, to achieve the same corresponding reduction

in ApoB-containing lipoproteins. However, the mean reduction in plasma triglyceride concentration in the fibrate trials was only 20 mg/dL to 50 mg/dL, a fraction of what would be needed to significantly reduce the risk of major vascular events within a short-term trial. Therefore, the results of the fibrate trials appear to be explained by the modest reductions in triglyceride level and therefore the modest corresponding reductions in ApoB-containing lipoproteins observed in these studies. Future randomized trials evaluating novel therapies that lower plasma triglyceride levels should be designed based on the net absolute reductions in ApoB-containing lipoproteins that can be achieved with those therapies, rather than on the corresponding therapeutic changes in triglycerides or LDL-C, particularly for therapies that alter plasma concentrations of both triglycerides and LDL-C either in the same or competing directions.

Limitations

This study has several limitations. First, this study compared triglyceride- and LDL-C-lowering genetic variants not lipid-lowering therapies. Second, genetic variants reflect the effect of lifelong changes in ApoB-containing lipoproteins on the risk of cardiovascular disease, which appear to be cumulative over time.^{5,34} As a result, the lower risk associated with lower triglycerides, LDL-C, and ApoB reported in this study is much larger than what have been reported for lipid-lowering therapies in randomized trials. However, having first established that the association between lifetime exposure to lower triglycerides and LDL-C on the risk of cardiovascular disease is approximately the same per unit lower level of ApoB-containing particles, it is reasonable to

Table 2. Association of Additional Genetic Scores With Triglycerides, LDL-C, and Risk of CHD per 10-mg/dL Lower Concentration of ApoB-Containing Lipoproteins^a

Composition of Genetic Score	Δ Triglycerides (95% CI)	Δ LDL-C (95% CI)	Odds Ratio for CHD (95% CI) per 10-mg/dL Lower ApoB
51 Variants associated with triglycerides at $P < 5.0 \times 10^{-8}$, but not LDL-C ($P > .001$)	-43.1 (-44.5 to -41.7)	-2.1 (-2.6 to -1.6)	0.762 (0.724 to 0.803)
59 Variants associated with LDL-C at $P < 5.0 \times 10^{-8}$, but not triglycerides ($P > .001$)	-2.1 (-3.0 to -1.1)	-15.5 (-15.8 to -15.1)	0.774 (0.748 to 0.800)
168 Variants associated with either triglycerides or LDL-C at $P < 5.0 \times 10^{-8}$	-21.6 (-22.1 to -21.1)	-11.8 (-12.0 to -11.6)	0.770 (0.757 to 0.783)
91 Variants associated with triglycerides at $P < 5.0 \times 10^{-8}$	-35.3 (-35.9 to -34.6)	-9.3 (-9.6 to -9.1)	0.776 (0.758 to 0.795)
100 Variants associated with LDL-C at $P < 5.0 \times 10^{-8}$	-17.5 (-18.0 to -17.0)	-13.5 (-13.7 to -13.3)	0.776 (0.762 to 0.791)
23 Variants associated with both triglycerides and LDL-C, both at $P < 5.0 \times 10^{-8}$, in same direction of effect	-32.3 (-33.0 to -31.5)	-12.0 (-12.3 to -11.7)	0.793 (0.771 to 0.815)
10 Variants associated with both triglycerides and LDL-C, both at $P < 5.0 \times 10^{-8}$, with opposite directions of effect	17.2 (16.0 to 18.4)	-22.5 (-23.0 to -22.1)	0.798 (0.767 to 0.830)
9 Variants associated with both triglycerides and LDL-C, both at $P < 5.0 \times 10^{-8}$, with opposite directions of effect (excluding <i>APOE</i> variant rs7412)	26.0 (23.7 to 28.3)	-20.3 (-21.2 to -19.4)	0.770 (0.711 to 0.833)

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

^a To compare the association of triglycerides and LDL-C with the risk of CHD for the same lower concentration of ApoB-containing lipoproteins not related to the *LPL* and *LDLR* genes, several additional genetic scores were constructed using up to 178 genetic variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium (GLGC). The data presented are for the associations of each genetic score with changes in triglycerides and LDL-C per 10-mg/dL lower ApoB in up to 305 699 participants in the GLGC and with the risk of CHD per 10-mg/dL lower ApoB in all 654 783 participants included in this study. For example, for each 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 51 variants associated with triglycerides but not LDL-C at genome-wide level of significance, there was a corresponding 41.3-mg/dL lower triglyceride level, 2.1-mg/dL lower LDL-C level, and a lower risk of CHD (odds ratio [OR], 0.762 [95% CI, 0.724-0.803]). By contrast,

for the same 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 59 variants associated with LDL-C but not triglycerides at genome-wide level of significance, there was a corresponding 15.5-mg/dL lower LDL-C level, 2.1-mg/dL lower triglyceride level, and a similar lower risk of CHD (OR, 0.774 [95% CI, 0.748-0.800]). Furthermore, for the same 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 168 variants associated with either triglycerides or LDL-C at genome-wide level of significance, there was a corresponding 21.6-mg/dL lower triglyceride level, an 11.8-mg/dL lower LDL-C level, and a similar lower risk of CHD (OR, 0.770 [95% CI, 0.757-0.783]). Despite being associated with different changes in lipids, all genetic scores were associated with similar lower risk of CHD for the same 10-mg/dL lower plasma ApoB concentration. The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the genetic scores are provided in eTable 7 in the [Supplement](#).

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD^a

Analysis	Variables	Odds Ratio for CHD (95% CI)	P Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849-0.875)	6.92E-65
Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model	Triglycerides	0.876 (0.850-0.902)	1.36E-14
	ApoB	0.761 (0.723-0.798)	7.51E-20
	LDL-C	1.010 (0.967-1.055)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

^a Data presented are derived from a multivariable meta-regression analysis of 186 genetic variants, including the 5 variants included in the *LPL* score, 3 variants included in the *LDLR* score, and 178 variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium. Effect sizes for the associated risk of CHD are reported per 10-mg/dL lower ApoB concentration, per 10-mg/dL lower LDL-C level, or per 50-mg/dL lower triglyceride level (because dividing triglyceride concentration by 5 estimates the cholesterol content carried by triglyceride-rich ApoB-containing lipoproteins as estimated by the Friedewald formula). In these analyses, the dependent variable was the effect estimate for risk of CHD in all 654 783 participants included in the study for each variant and the independent variables were the effect estimates for the associated changes in plasma triglycerides, LDL-C, and ApoB, measured in up to 305 699 participants in Global Lipids Genetics Consortium for each variant. The analysis

was weighted by the inverse squared standard error of the associated risk of CHD for each variant and forced to pass through the origin. For example, in multivariable mendelian randomization analyses involving these 186 genetic variants, both triglycerides (odds ratio [OR], 0.876 per 50-mg/dL lower triglycerides) and LDL-C (OR, 0.862 per 10-mg/dL lower LDL-C) were independently associated with a lower risk of CHD at genome-wide level of significance. By contrast, when ApoB was included in the multivariable mendelian randomization analyses, the associations with CHD for both triglycerides (OR, 1.014 per 50-mg/dL lower triglycerides) and LDL-C (OR, 1.010 per 10-mg/dL lower LDL-C) became null, but the association per 10-mg/dL lower ApoB remained unchanged (OR, 0.761 per 10-mg/dL lower ApoB). The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the analysis are provided in eTable 7 in the [Supplement](#). Additional multivariable meta-regression analyses for various combinations of these variants is provided in eTable 8 in the [Supplement](#).

then anticipate that short-term pharmacologic reductions in plasma triglyceride and LDL-C levels will be associated with the same lower risk of cardiovascular events per unit change in ApoB.²¹ Third, this study specifically estimates the clinical benefit of the lipid-lowering effect of therapies that reduce plasma triglycerides, LDL-C, or both, but not the other potential pleiotropic effects that a therapy may have on the risk of cardiovascular disease. Indeed, the reported reductions in cardiovascular events in the JELIS and REDUCE-IT trials were far greater than what would have been expected from the modest observed changes in plasma lipid levels, thus suggesting that the observed

clinical benefit of the omega-3 fatty acid eicosapentaenoic acid may be largely due to its non-lipid-related effects.^{35,36}

Conclusions

Triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

ARTICLE INFORMATION

Accepted for Publication: December 17, 2018.

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Author Contributions: Dr Ference had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ference, Kastelein, Ray, Ginsberg, Packard, Chapman, Oliver-Williams, Wood, Butterworth, Di Angelantonio, Danesh, Nicholls, Bhatt, Sabatine. **Drafting of the manuscript:** Ference, Packard, Laufs. **Critical revision of the manuscript for important intellectual content:** Ference, Kastelein, Ray, Ginsberg, Chapman, Laufs, Oliver-Williams, Wood, Butterworth, Di Angelantonio, Danesh, Nicholls, Bhatt, Sabatine, Catapano.

Statistical analysis: Ference, Packard, Oliver-Williams, Wood.

Obtained funding: Ference, Butterworth, Di Angelantonio.

Administrative, technical, or material support: Danesh, Nicholls.

Supervision: Ference, Kastelein, Ray, Butterworth, Catapano.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ference reported receiving personal fees from Merck & Co, Amgen, Esperion Therapeutics, Regeneron, Sanofi, Pfizer, dalCOR, The Medicines Company, Civi BioPharma, KRa Pharmaceuticals, American College of Cardiology, European Society of Cardiology, and the European Atherosclerosis Society and grants from Merck & Co, Amgen, Novartis, and Esperion Therapeutics. Dr Kastelein reported receiving personal fees from Affiris, Amgen, Corvidia, CSL Behring, Civi Biopharma, Esperion, Gemphire, Madrigal, The Medicines Company, North Sea Therapeutics, Novartis, Regeneron, Staten Biotech, Merck & Co, Eli Lilly, Roche, Pfizer, and Dezima. Dr Ray reported receiving personal fees from Sanofi, Amgen, Regeneron, Merck Sharp & Dohme, Cipla, Cerenis, Akcea, Eli Lilly, The Medicines Company, AstraZeneca, Pfizer, Kowa, Algorithm, IONIS, Esperion, Novo Nordisk, Takeda, Boehringer Ingelheim, Resverlogix, and Abbvie and grants from Merck & Co, Merck Sharp & Dohme, Sanofi, Regeneron, Pfizer, and Amgen. Dr Ginsberg reported receiving personal fees and grants from Merck & Co, Kowa, Sanofi, Regeneron, Esperion, Akcea, and Amgen. Dr Chapman reported receiving personal fees from Akcea, Alexion, Amarin, Amgen, Daiichi-Sankyo, Kowa, Merck & Co, Pfizer, Sanofi, Regeneron, and Unilever and grants from Amgen, CSL, Kowa, Merck & Co, and Pfizer. Dr Packard reported receiving personal fees from Merck Sharp & Dohme, Merck & Co, Amgen, Pfizer, Sanofi, Regeneron, and Daiichi-Sankyo. Dr Laufs reported receiving personal fees from Merck & Co, Amgen, Pfizer, Esperion, and Sanofi. Dr Oliver-Williams reported receiving prize money from Novartis. Dr Butterworth reported receiving grants from the UK Medical Research Council, British Heart Foundation, European Union Framework Programme 7, and the National Institute for Health during the conduct of the study and grants from Pfizer, AstraZeneca, Merck & Co, Novartis, Biogen, and the European Research Council. Dr Di Angelantonio reported receiving grants from the National Institute for Health Research, Medical Research Council, British Heart Foundation, and NHS Blood and Transplant. Dr Danesh reported receiving personal fees from Merck Sharp & Dohme, Merck & Co, Novartis, Pfizer, and Sanofi; nonfinancial support from diaDexus; and grants from the British Heart Foundation, Bupa Foundation, diaDexus, European Research Council, European Union, Evelyn Trust, Fogarty International Center, GlaxoSmithKline, Merck & Co, National Heart, Lung, and Blood Institute, National Institute for Health Research, National Institute of

Neurological Disorders and Stroke, NHS Blood and Transplant, Novartis, Pfizer, AstraZeneca, UK Medical Research Council, Wellcome Trust, and the UK Biobank. Dr Nicholls reported receiving personal fees from Eli Lilly, AstraZeneca, Amgen, Anthera, Omthera, Takeda, Novartis, Resverlogix, Sanofi, Regeneron, Esperion, Merck, Boehringer Ingelheim, CSL Behring, and Roche and grants from Eli Lilly, AstraZeneca, Amgen, Anthera, InfraRedx, LipoScience, Novartis, Resverlogix, Sanofi, Regeneron, Cerenis, Esperion, Merck & Co, and The Medicines Company. Dr Bhatt reported receiving grants from Amarin during the conduct of the study; grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, Roche, Pfizer, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Eli Lilly, Chiesi, Ironwood, Abbott, Regeneron, PhaseBio, Idorsia, Synaptic, and The Medicines Company; personal fees or nonfinancial support, including travel and lodging, from FlowCo, Plx Pharma, Takeda, Medscape Cardiology, Regado Biosciences, Boston VA Research Institute, Clinical Cardiology, VA, St Jude Medical (now Abbott), Biotronik, Cardax, the American College of Cardiology, Boston Scientific, Merck, Svelte, and Novo Nordisk; personal fees from Duke Clinical Research Institute, Mayo Clinic, Population Health Research Institute, American College of Cardiology, Belvoir Publications, Slack Publications, WebMD, Elsevier, the Society of Cardiovascular Patient Care, HMP Global, Harvard Clinical Research Institute (now Baim Institute for Clinical Research), *Journal of the American College of Cardiology*, Cleveland Clinic, Mount Sinai School of Medicine, TobeSoft, Boehringer Ingelheim, and Bayer; and nonfinancial support from the American Heart Association outside the submitted work. Dr Sabatine reported receiving personal fees from Amgen, AstraZeneca, Bristol-Myers Squibb, Dyrnamix, Intarcia, Merck & Co, Janssen Research Development, MedImmune, Alnylam, CVS Caremark, Ionis, Cubist, Esperion, The Medicines Company, Myokardia, and Zeus Scientific and grants from Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Intarcia, Merck & Co, Roche Diagnostics, Takeda, Novartis, Poxel, Janssen Research and Development, MedImmune, Eisai, Genzyme, and Pfizer. Dr Catapano reported receiving personal fees from AstraZeneca, Amgen, Aegerion, Genzyme, Sanofi, Merck & Co, Menarini, Kowa, and Pfizer and grants from Amgen, Eli Lilly, Genzyme, Mediolanum, Sanofi, Merck & Co, Pfizer, Regeneron, Rottapharm, Recordati, and Sigma tau. No other disclosures were reported.

Funding/Support: Dr Ference is supported by the National Institute for Health Research Cambridge

Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust. Dr Oliver-Williams is supported by Homerton College, University of Cambridge. Dr Butterworth is supported by the European Research Council. Dr Danesh is supported by the Medical Research Council, British Heart Foundation, and the National Institute for Health Research.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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